Combination therapy using anticancer drug and antiadhesive peptide FNIII14 overcomes cell adhesion-mediated drug resistance of acute myelogenous leukemia

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Acute myelogenous leukemia (AML) cells are generally chemosensitive, and 70-80% of AML patients undergo complete remission. Unfortunately long-term, disease-free survival remains as low as 30-50%, mainly because of relapses after chemotherapy. Improved survival requires new strategies to prevent relapse. Bone-marrow minimal residual disease (MRD) causes relapse after chemotherapy in patients with AML. We postulate that the drug resistance is induced by the attachment of VLA-4 on leukemic cells to fibronectin on bone-marrow stromal cells. We found that VLA-4-positive cells acquired resistance to anoikis or drug-induced apoptosis through the PI-3K/Akt/Bcl-2 signaling pathway, which is activated by the interaction of VLA-4 and fibronectin and the complete remission rate for the VLA-4-positive patients was lower than that of VLA-4-negative patients. These results suggest that the inhibiting factor that inhibits the interaction between VLA-4 on AML and stromal fibronectin may exterminate AML cells on MRD by the combination therapy with anti-cancer drug. We also demonstrate that anti-adhesive peptide FNIII14 derived from fibronectin suppresses VLA-4-mediated cell adhesion to fibronectin by inactivation of beta1 integrin. In this study we achieved a 100% survival rate by combining FNIII14 and cytosine arabinoside in a mouse model of MRD, whereas the cytosine arabinoside alone prolonged survival only slightly. Thus, FNIII14 is useful for overcoming cell adhesion-mediated drug resistance of AML as a molecular targeting therapy.